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Enteric coating of hard gelatin capsules. Part 2—Lioavailability of formaldehyde treated capsules

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Abstract

Part 1 of this article defined the prerequisites which allow the gastro-resistance stabilization of formaldehyde treated capsules. Part 2 examines the dissolution profiles of these capsules with different contents. This set of experiences allowed an evaluation of the quality, potentialities and limitations of the developed coating process. The contents choice considered different solubilities because this is one of the most important parameters that affect the release rate from capsules. © 1997 Elsevier Science B.V.

Keywords: Capsules; Enteric coating; Formaldehyde; Disintegration; Drug release; Stability

1. Introduction

Part 1 of this study evaluated the influence of different parameters on gastro-resistance of formaldehyde treated capsules along with the quantification of formaldehyde on different phases and under different process conditions. Finally, the conditions which allow the enterossolubility stabilization of the capsules were defined (Pina, 1994; Pina et al., 1996). Part 2 examines the dissolution profiles of formaldehyde treated capsules with different contents, which lead to different release models in accordance with its physical and chemical characteristics and the coating conditions.

It was the use of 'in vitro' dissolution equipment that allowed the examination of drug release, as a function of time under analogous physiological conditions, evaluating rigorously the qualities of the developed coating process.

The two important requirements for presentation of drugs in hard gelatin capsules are that the correct dose must be contained within the volume of the capsule shell and that the drug must be released from the capsule, at the required rate, when administered to the patient (Newton and Razzo, 1977a,b; Newton, 1987). Because release of a drug from the dosage form into the gas-

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trointestinal fluids is an essential first step in drug absorption and bioavailability, dissolution is a critical parameter in determining the performance and defining the quality of solid oral products (Murthy and Ghebre-Sellassie, 1993; Möller and Wirbitzki, 1993).

The results from Part 1 of this study provide evidence for the influence of the content in gastroresistance of the formaldehyde treated capsules. It was considered important to examine the feasibility of employing this coating to drugs whose solubilities in gastric juice presented discriminate values with the finality of verifying the potentialities and the limitations of the studied process. Effectively, for many drugs, the solubility data may be used as a basis for making practical decisions concerning the absorption of a drug from a formulation (Hamlin et al., 1965).

We selected acetylsalicylic acid, theophylline, paracetamol, propranolol hydrochloride, isoniazid, ranitidine hydrochloride and procainamide hydrochloride as model drugs to establish a decreasing scale of data solubility, because this is the major factor controlling release of drug from capsules. The order of magnitude of the effect is given in Noyes Whitney's equation (Noyes and Whitney, 1897). The departures from this relation are no doubt due to involvement of physical factors, such as disintegration and deaggregation of the powder mass within the capsules (Newton and Razzo, 1977a,b).

Table 1
Solubilities of the utilized drugs

Drug	Solubility (g/ml)	
	Gastric juice	Water
Acetylsalicylic acid	0.0032	0.0033
Theophylline	0.0070	0.0080
Paracetamol	0.0150	0.0140
Propranolol hydrochloride	0.0520	0.0500
Isoniazid	0.1280	0.1250
Ranitidine hydrochloride	0.6500	0.2500
Procainamide hydrochloride	2.6310	4.0000

2. Materials and methods

2.1. Materials

The materials employed were as follows: 0 hard gelatin capsules (colourless; Capsugel). Acetylsalicylic acid (125–400 μm, Bayer); anhydrous theophylline (125–500 μm, Boehringer); paracetamol (< 200 μm, Hoechst); propranolol hydrochloride (90–400 μm, Bechpharma); isoniazid (125–400 μm, Sigma); ranitidine hydrochloride (125–500 μm, supplied by Bial Laboratory); procainamide hydrochloride (90–400 μm, Sigma) and talc (63–90μm). Simulated gastric and enteric juice (USPXXII). Ethyl alcohol 75% (v/v); formaldehyde (36.6% w/w) and sodium hydroxide, all proanalyze (Merck).

Table 2
Composition of capsule formulations

Ingredient (mg)	Formulation						
	I	II	III	IV	V	VI	VII
Acetylsalicylic acid	476						
Theophylline		425					
Paracetamol			350				
Propranolol hydrochloride				20			
Isoniazid					156		
Ranitidine hydrochloride						150	
Procainamide hydrochloride							141
Talc					423	468	450

Table 3
Coating solutions

Formulations	Hydroalcoholic formaldehyde solution
I	3.0%, 75% (v/v)
II	3.5%, 75% (v/v)
III	6.0%, 75% (v/v)
IV	15.0%, 70% (v/v)
V	15.0%, 70% (v/v)
VI	16.0%, 60% (v/v)
VII	20.0%, 60% (v/v)

The solubilities of drugs in gastric juice and water are described in Table 1.

2.2. Formulations

The composition of the different capsules is presented in Table 2. The capsules were filled manually and sealed by banding with aqueous solution of gelatin (10%) (Pina, 1994; Pina et al., 1996).

2.3. Coating solutions

Hydroalcoholic solutions of formaldehyde applied in coating of formulations are described in Table 3.

2.4. Coating procedure

Capsules of different formulations (0) were subjected to the following regime:

(1) Formaldehyde treatment: coating solutions defined in 2.3, immersion time in formaldehyde solution was 15 min.

(2) First drying at 37°C for 30 min plus washing in alcohol with same alcohol content of the formaldehyde solution for 15 min, plus a second drying at 37°C for 30 min plus 15.5 h at ambient temperature.

These conditions, which allowed satisfactory gastro-resistance and enterossolubility properties of capsules, were founded in previous disintegration and dissolution tests, taking into consider ation that not more than 10% of the active ingredient should be released from capsules on 'in vitro' dissolution in gastric juice (2 h), and that in a subsequent test using enteric juice (0.75 h), not less than 75% of the active ingredient should be dissolved (Möller and Wirbitzki, 1990; US Pharmacopeia XXII, 1990).

2.5. Characteristics of the formulations

The appearance of capsule shells and contents were observed. The weight uniformity was determined as described in FPV (Farmacopeia Portuguesa V, 1986).

2.6. Quantification of free and residual formaldehyde

The values of free and residual formaldehyde were, respectively, analysed in 'washing' alcohol and after the second drying by HPLC measurements (Pina et al., 1995, 1996).

2.7. Quantification of active substances

Drug concentrations in gastric and enteric juices from the formulations were determined spectrophotometrically (Brewer, 1977; Embil and Toronsian, 1979; Hohnjec et al., 1981, 1986; Simons et al., 1984; Clarke, 1986; Plaizer-Vercammen and Suenens, 1991; Garcia, 1992; Babar et al., 1992).

2.8. Disintegration testing

Disintegration time of capsules was evaluated as previously described in Part 1 of this study.

2.9. Dissolution testing

Capsules of different formulations (attached with a few turns of wire helix that would otherwise float) were subjected to dissolution testing using a dissolution apparatus with rotative paddle (Hanson Research). They were tested for 2 h in artificial gastric fluid maintained at 37°C and the speed used was 50 rpm. After this time, the intact capsules were first rinsed in water and immediately immersed in enteric juice for 75 min. Filtered samples were withdrawn and analysed spectrophotometrically, at regular intervals.

Table 4
'Free' formaldeyde in washing alcohol

Batches	Free formaldehyde (mg/capsule)	S	Cv%
Acetylsalicylic acid	0.438 ± 0.0027	0.022	4.95
Theophylline	0.476 ± 0.0012	0.010	2.02
Paracetamol	0.825 ± 0.010	0.008	0.96
Propranolol hydrochloride	2.230 ± 0.150	0.120	5.40
Isoniazid	2.256 ± 0.111	0.089	3.95
Ranitidine hydrochloride	2.502 ± 0.018	0.015	0.59
Procainamide hydrochloride	3.100 ± 0.196	0.158	5.10

Table 5
Residual formaldeyde after second drying

Batches	Residual formaldehyde mg/caps			
	After coating	1 month	3 months	6 months
Acetylsalicylic acid	0.335 ± 0.012	0.083 ± 0.003	0.047 ± 0.002	0.042 ± 0.004
Theophylline	0.297 ± 0.018	0.079 ± 0.003	0.053 ± 0.003	0.048 ± 0.002
Paracetamol	0.324 ± 0.007	0.117 ± 0.006	0.065 ± 0.005	0.066 ± 0.005
Propranolol hydrochloride	0.800 ± 0.020	0.296 ± 0.005	0.141 ± 0.009	0.134 ± 0.006
Isoniazid	0.817 ± 0.012	0.299 ± 0.004	0.135 ± 0.004	0.130 ± 0.008
Ranitidine hydrochloride	0.842 ± 0.003	0.313 ± 0.013	0.145 ± 0.005	0.143 ± 0.012
Procainamide hydrochloride	1.021 ± 0.032	0.364 ± 0.014	0.168 ± 0.009	0.161 ± 0.005

2.10. Stability studies

Residual formaldehyde, disintegration and dissolution tests were determined on capsules coated under conditions described in Section 2.4, immediately after coating and in the end of 1, 2, 3 and 6 months of holding the capsules packed in plastic bottles, well stoppered, at ambient temperature and with a relative humidity of 40–50%.

3. Results and discussion

3.1. Characteristics of the formulations

During this study, the capsules didn't present modifications on its physical characteristics (deformation, hardening or softening of gelatinous shell) and its content was unchangeable (without aggregation).

Relating to weight uniformity the determined values were in accordance with the defined limits established in FPV (Farmacopeia Portuguesa V, 1986).

3.2. Determination of 'free ' and residual formaldehyde

The results from Tables 4 and 5 demonstrate that, for all model drugs, the increase of formaldehyde concentration in coating solution promotes higher values of 'free 'and residual formaldehyde, validating the previous results. On the other hand, residual formaldehyde changed on inverse ratio of ageing time but from 3 months of storage on, the stabilization is evident. These results are in accordance with Part 1. The residual formaldehyde concentration doesn't constitute any difficulty for capsules administration (WHO, 1989).

Table 6
Disintegration time in enteric juice

Batches	Disintegration time (min)			
	After coating	1 month	3 months	6 months
Acetylsalicylic acid	8.7 ± 0.3	8.3 ± 0.7	8.4 ± 0.5	8.9 ± 0.8
Theophylline	13.6 ± 1.4	14.0 ± 1.9	15.2 ± 1.0	14.0 ± 1.5
Paracetamol	24.8 ± 1.0	25.0 ± 0.9	25.0 ± 0.9	25.4 ± 1.1
Propranolol hydrochloride	35.2 ± 2.7	34.2 ± 3.4	35.2 ± 4.0	32.6 ± 4.6
Isoniazid	25.0 ± 2.8	26.2 ± 3.4	25.8 ± 3.0	28.0 ± 4.1
Ranitidine hydrochloride	29.4 ± 4.2	29.2 ± 2.2	27.2 ± 2.7	26.6 ± 2.8
Procainamide hydrochloride	32.8 ± 5.6	33.6 ± 4.4	36.0 ± 5.1	38.4 ± 3.9

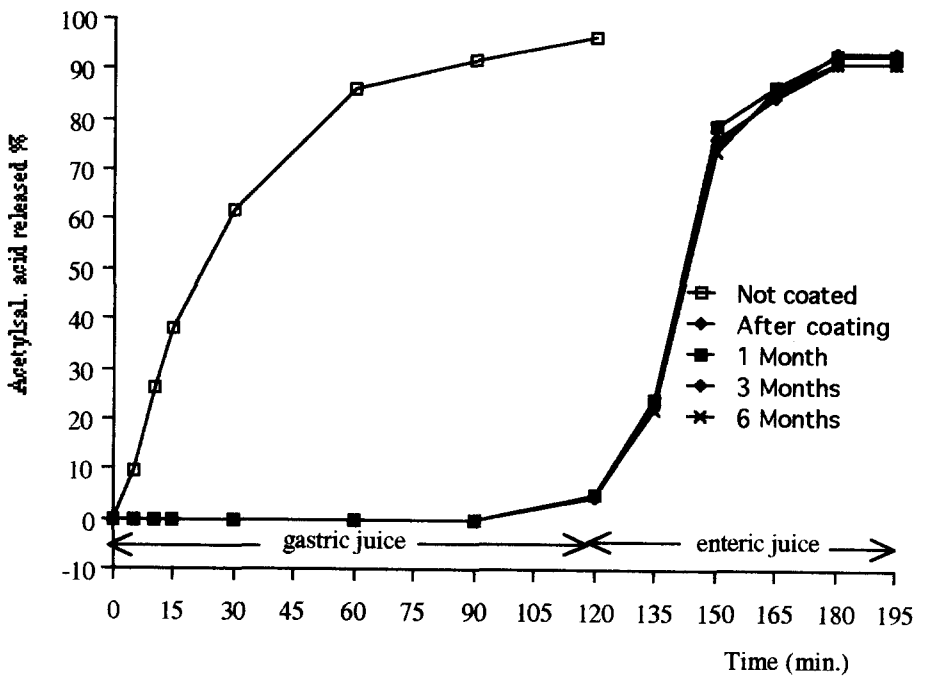

Fig. 1. Dissolution profile of acetylsalicylic acid capsules

3.3. Disintegration time of formulations

Table 6 shows that disintegration time of capsules in enteric juice was constant during storage, for all formulations.

3.4. Dissolution time of formulations

The results related to dissolution profiles of the studied formulations are presented in Table 7 and Figs. 1–7. Analysing the described results, we can extract the next global deductions: the developed coating made possible the obtention of capsules with good gastro-resistance, presenting for all experimented model drugs a release in gastric juice lower than 10% and acceptable results in enteric juice. According to the content's solubility, that changed from slightly soluble to soluble (acetylsalicylic acid, theophylline, paracetamol and propranolol hydrochloride), it was necessary to apply

Table 7
Synthesis of results from bioavailability

Drugs	Gastric juice solubility (g/ml)	Formaldehyde concenctration (% w/w)	Gastric juice release	Enteric juice release		Adjuvant
			%	Time (min)	%	
Acetylsalicylic acid	0.0032	3	<5	45	>85	—
Theophylline	0.0070	3.5	5	60	80	—
Paracetamol	0.0150	6	8.5	45	>75	—
Propranolol hydrochloride	0.0520	15	7.5	75	75	—
Isoniazid	0.1280	15	7	75	>75	Talc
Ranitidine hydrochloride	0.6500	16	7	45	75	Talc
Procainamide hydrochloride	2.6310	20	8	90	75	Talc

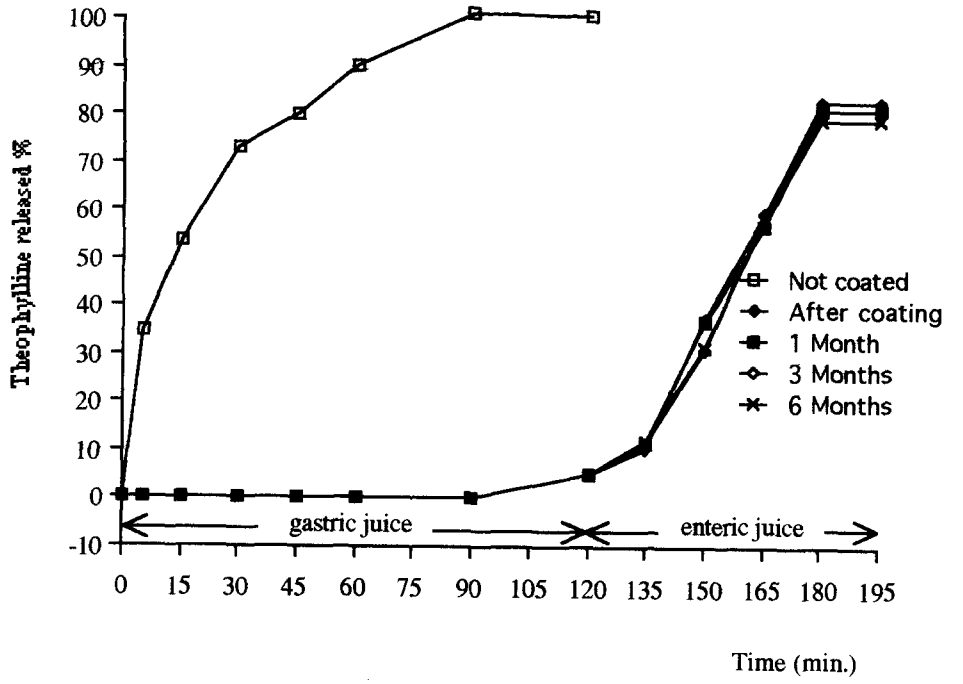

Fig. 2. Dissolution profile of theophylline capsules

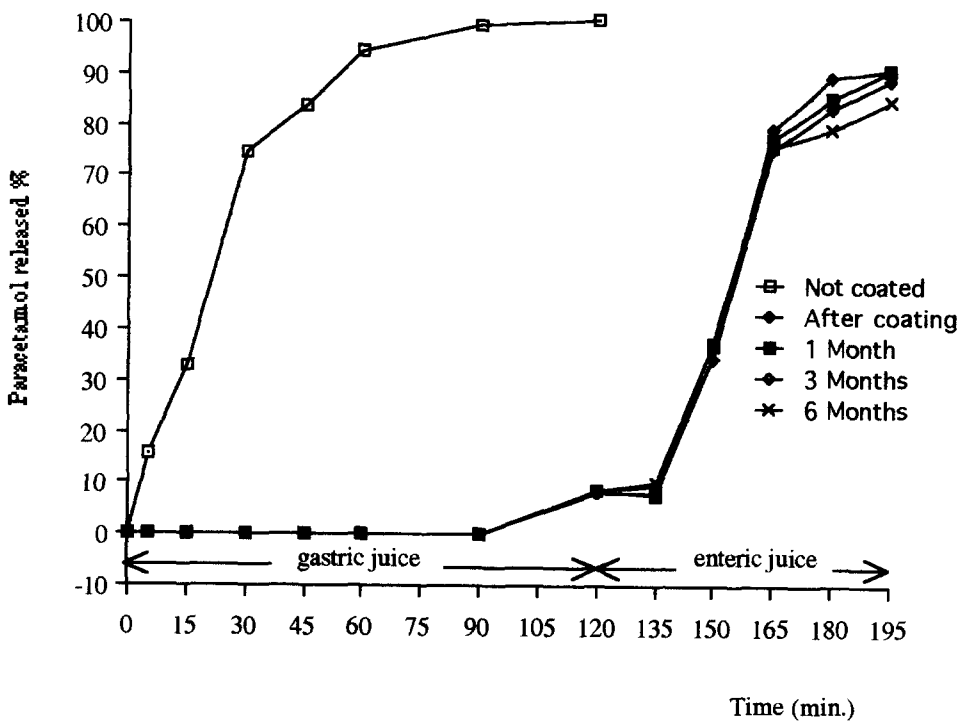

Fig. 3. Dissolution profile of paracetamol capsules

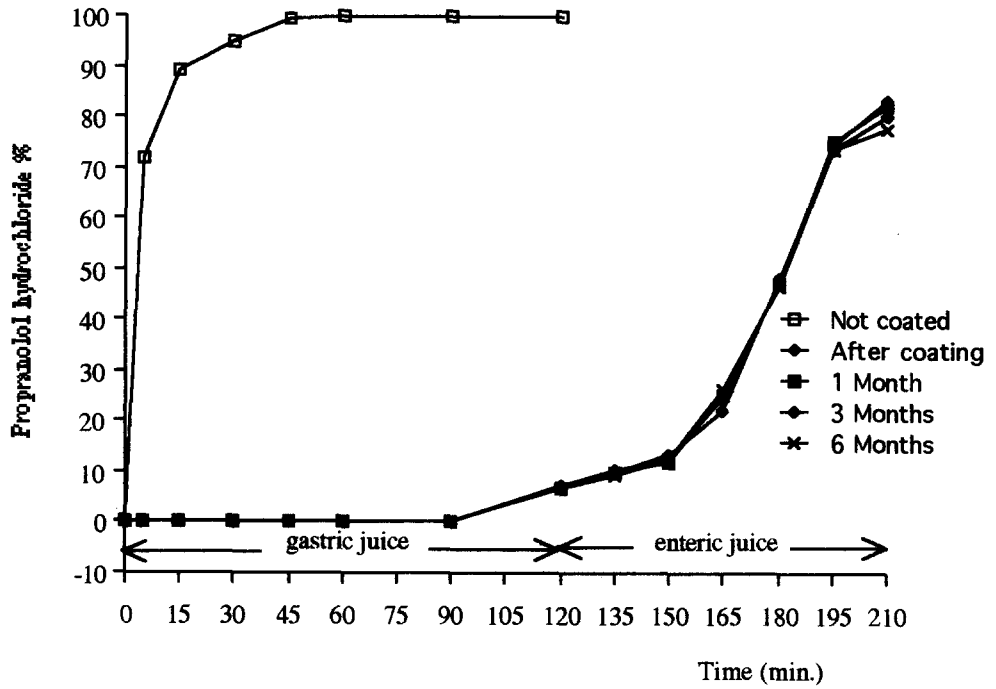

Fig. 4. Dissolution profile of propranolol hydrochloride capsules

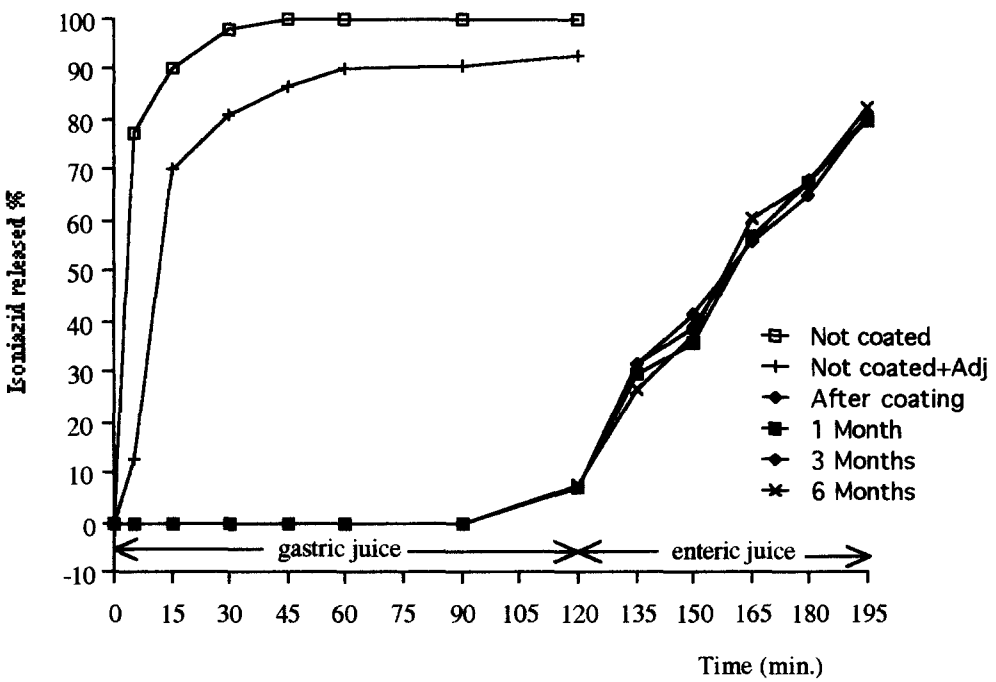

Fig. 5. Dissolution profile of isoniazid capsules

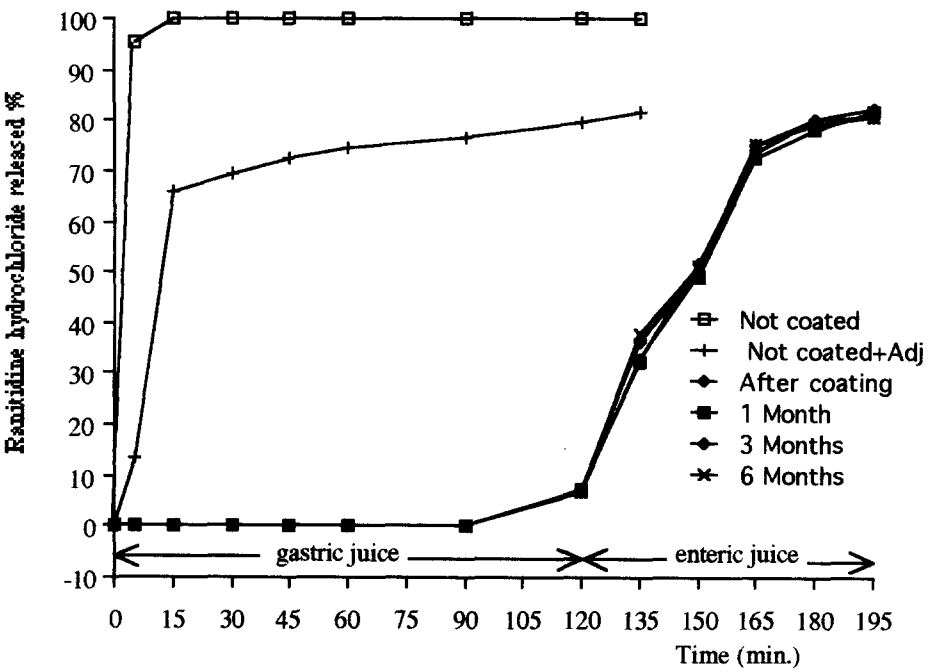

Fig. 6. Dissolution profile of ranitidine hydrochloride capsules

coating solutions with increasing formaldehyde concentrations, using the same conditions of treatment for the preparation of capsules with adequate gastro-resistance characteristics.

These results allowed the establishment of a relation between drug's solubility in gastric juice (S), and formaldehyde concentration in coating solution (C). It is:

$$C = 248.556S + 2.101 \quad (r = 0.999)$$

where C is the formaldehyde concentration and S is the drug's solubility in gastric juice which is shown in Fig. 8.

To validate the previous relation, capsules containing two new drugs (codeine and caffeine) were prepared. For each one an own methodology was developed. The solubilities in gastric juice were 0.045 and 0.050 g/ml, respectively, for codeine and caffeine (Hamlin et al., 1965). Formaldehyde solutions (14%; 75% v/v) and (15%; 75% v/v) were applied (in the same conditions to those used in drug models) for obtention of its gastro-resistant coating. The results are described in Table 8 and its analyses demonstrate that formaldehyde concentration in coating solution (experimental and theoretical) do not present significative differences, validating the defined mathematical quantitative relation. Considering the solubility of any drug which it is important to render gastro-resistant, it is possible to predict the adequate

Table 8
Equation validation

Drugs	C % (w/w)	S (g/ml)	C^a % (w/w)	Release % in gastric juice
Codeine	14	0.045	13.3	8.0 ± 0.69
Caffeine	15	0.050	14.6	8.8 ± 0.72

C, formaldeyde concentration; S, Solubility of drugs in gastric juice; C^a, Calculated concentration from equation.

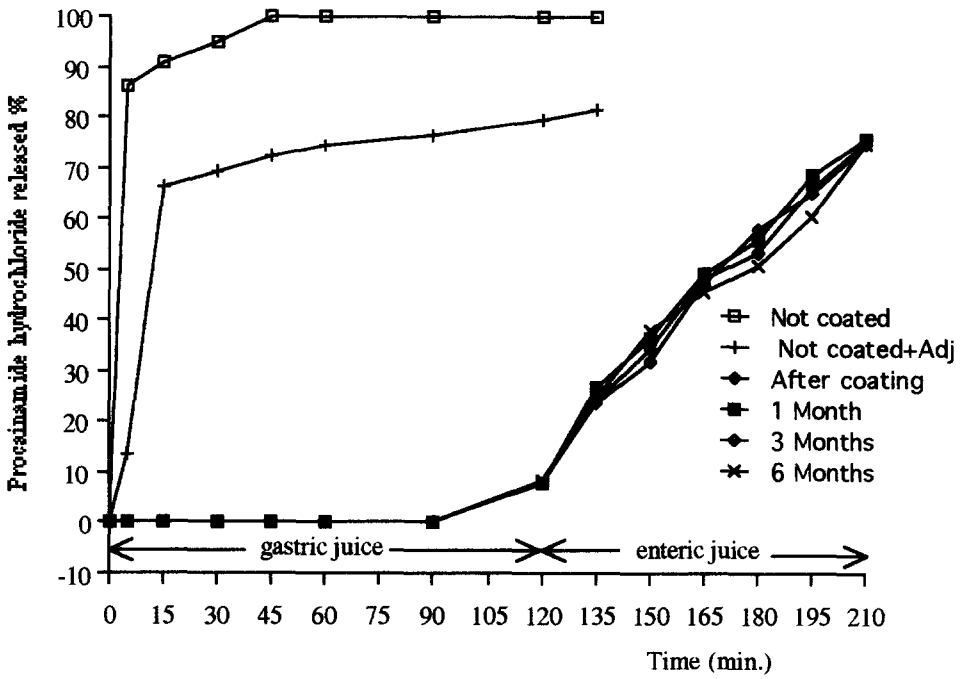

Fig. 7. Dissolution profile of procainamide hydrochloride capsules

formaldehyde concentration, by interpolation in the previous equation. For drugs freely and very soluble (isoniazid, ranitidine hydrochloride and procainamide hydrochloride) it was necessary to ensure the inclusion of adjuvants on the pharmaceutical dosage form that—by its hydrophobic

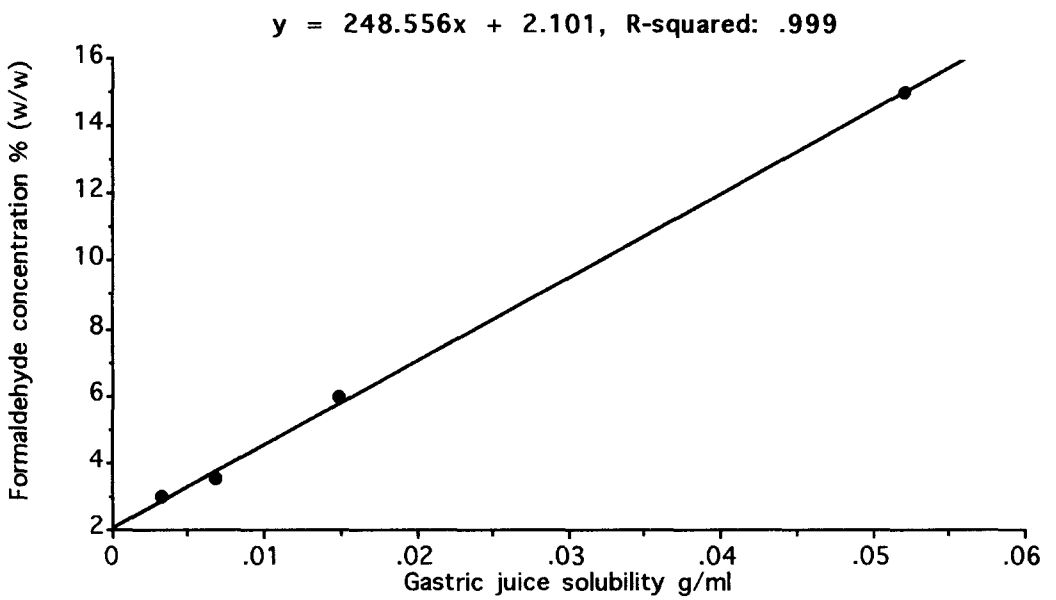

Fig. 8. Relation between drug's solubility in gastric juice and formaldehyde concentration of coating solution

nature of difficult disintegration and dissolution—allows an adequate gastro-resistance.

3.5. Stability studies

Analysing the identical results of residual formaldehyde, disintegration and dissolution times for all batches of capsules after 1, 3 and 6 months of storage at ambient temperature, we verify a stabilization of coating process.

4. Conclusions

The results presented here allow us to conclude that: the developed coating can be directly applied to gelatin capsules containing very slightly soluble, slightly soluble and soluble drugs in gastric juice, being necessary to use higher concentrated formaldehyde coating solutions, when the drug's solubility increases; it is possible to define a linear relation between solubility of very slightly soluble, slightly soluble and soluble drugs and formaldehyde concentration of coating solution by the equation: $C = 248.556S + 2.101$, where C is the formaldehyde concentration and S is the drug's solubility in gastric juice; for freely and very soluble drugs it is indispensable to introduce adjuvants that by their hydrophobic nature allow adequate gastro-resistance; the study of lioavailability from capsules containing several drugs, chosen in accordance with a decreasing scale of solubility of contents, demonstrate that the developed coating allows the obtention of good gastro-resistance, with a drug release in gastric juice lower than 10% and enteric dissolution levels very acceptable after coating and during storage of capsules.

From the results of Part 1 and Part 2 of this study, it's possible to affirm that the application of hydroalcoholic solutions of formaldehyde constitutes a simple, stable, reproducible and inexpensive method for the preparation of gastro-resistant capsules, being a valid alternative to those which have been proposed.

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